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Serial studies of pulmonary stenosis in infancy and childhood[1]

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Thirty-five children with pulmonary stenosis were catheterized from 1 day to 9 years of age and recatheterized after 2 weeks to 15 years. Right ventricular systolic pressure rose in 24 and the increase was greater in those under than over 5 years old. Pulmonary valve orifice area per square metre of body surface area increased in 12, did not change in 3, and fell in 17; absolute decrease in calculated orifice area was usually associated with infundibular hypertrophy. Increase in right ventricular systolic pressure with age was thus caused by failure of the valve orifice to grow fast enough to keep pace with the increase of stroke volume.

In the whole group, increasingly severe pulmonary stenosis was matched by increasing electrocardiographic evidence of right ventricular hypertrophy. However, in individual patients the electrocardiogram could suggest that right ventricular pressure had decreased when in fact it had risen considerably.

Severe pulmonary stenosis may cause congestive heart failure and death in infancy or early childhood (Benton *et al.*, 1962; Luke, 1966; Gersony *et al.*, 1967). However, relatively few of those born with pulmonary stenosis follow this course (Carlgren, 1959; Rowe and Cleary, 1960; Lambert, Canent, and Hohn, 1966) and the majority of deaths have occurred in older children and adults (Selzer *et al.*, 1949; Abrahams and Wood, 1951; Fabricius, 1959). Most of the reported older patients with severe pulmonary stenosis did not have serial cardiac catheterizations and we do not know if they had from infancy a tight stenosis that was well tolerated for many years, or if the obstruction was mild in infancy and became more severe with time.

There have been few serial catheterization studies of the natural history of pulmonary stenosis in children and even fewer in very young children. Out of a total of 105 recatheterized patients cited in 8 reports (Fabricius, 1959; Engle, Ito, and Goldberg, 1964; Tinker *et al.*, 1965; Levine and Blumenthal, 1965; Moller and Adams, 1965; Loogan, Gleichmann, and Wilke, 1966; Lueker, Vogel, and Blount, 1970; Møller, Wennevold, and Lyngborg, 1973), the right ventricular pressure had risen significantly in the second study in only 15, almost all of whom had high pressures at the first study. Furthermore, most of the patients were older children and adults; only 15 were under 5 years at the time of the first study and none were infants. The general lack of change of right ventricular pressure with time suggests that the pulmonary valve area increased with age in most of these patients, and this was confirmed by calculations of the valve area in 2 of these studies (Moller and Adams, 1965; Lueker *et al.*, 1970). While this information is important it does not throw any light on the changes occurring in the few with increasingly severe disease.

There are several ways in which pulmonary stenosis might become more severe. Some studies (Kirklin *et al.*, 1953; Johnson, 1959; Little, Lavender, and DeSanctis, 1963) have suggested progressive obstruction of the right ventricular outflow tract from increasing hypertrophy of infundibular muscle but these have all been in older children and adults. Campbell and Missen (1969) speculated that fibrin deposited on a stenotic valve could diminish the orifice area. Finally, Engle and Taussig (1950) considered that the orifice of a stenotic pulmonary valve might remain the same size and so become relatively smaller as body size and cardiac output increased with growth. This might explain why Tinker *et al.* (1965) noted that, when there was electrocardiographic evidence of deterioration in

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patients with pulmonary stenosis, it usually took place during the adolescent growth spurt.

Because of the lack of information about the changes that take place in pulmonary stenosis in younger children, we here report serial clinical and cardiac catheterization studies of 35 infants and young children with congenital pulmonary stenosis.

Subjects and methods

Thirty-five children were first catheterized between 1 day and 9 years of age, and recatheterized at intervals ranging from 2 weeks to 15 years; 6 children had third catheterizations. Twelve were seen at the Bronx Municipal Hospital Center or Lincoln Hospital in New York, 13 at the New York University Medical Center, and 10 at the University of California-San Francisco. One of the 17 girls and 1 boy had Noonan's syndrome.

All had valvar pulmonary stenosis with an intact ventricular septum. Two with rubella embryopathy had added mild peripheral pulmonary arterial stenosis. Three had small left-to-right shunts with pulmonary to systemic flow ratios of 1:8, 1:3, and 1:2; one shunt was at the atrial level, one through a persistent ductus, and one at both levels.

No sedation or anaesthesia was used for 8 infants catheterized under 3 months of age; 10 other infants received general anaesthesia (5) or sedation with tribromoethyl alcohol (3), morphine sulphate (1), or chloral hydrate (1). The remainder were usually premedicated with pethidine and hydroxyzine hydrochloride, each 1 mg/kg intramuscularly, and were never deeply sedated though they were usually quiet throughout the study.

Oxygen uptake was measured in 3 infants with a nasal valve (Golinko and Rudolph, 1961) and in most over 7 years of age by collection of expired air. For the others, oxygen uptake was estimated from average values for heart rate and body surface area (Hoffman and Rudolph, 1965; LaFarge and Miettinen, 1970); the 95 per cent confidence limits for these assumed values are about 50 per cent each side of the mean value. Oxygen saturations were measured spectrophotometrically by a modified Drabkin method (Rudolph and Cayler, 1958) or, more recently, by reflectance oximetry. Flows were calculated by the Fick principle. Whenever possible, pressures in the pulmonary artery and right ventricle were measured using a catheter with one or more side holes. The reference level for all pressures was the midchest.

The area of the pulmonary valve orifice was estimated by the formula of Gorlin and Gorlin (1951); the flow across the valve was the pulmonary blood flow in all but the patient with the ductal shunt, in whom systemic flow was used. When there was infundibular stenosis, the same formula was used to indicate effective orifice area. In some infants catheterized at other hospitals, the pressure tracings were not available for calculating systolic ejection time and the mean pressure difference from right ventricle to pulmonary artery. We then used the formula of Bassingthwaighte *et al.* (1963) to derive the mean systolic pressure difference, or the formula of Moller and Adams (1966) to calculate pulmonary valve area from pulmonary valvar resistance.

At the first cardiac catheterization, 5 children (1 a neonate) had peak right ventricular systolic pressures at or under 35 mmHg (4.7 kPa); the mean systolic pressure differences across the pulmonary valves ranged from 6 to 18 mmHg (0.8 to 2.4 kPa). All had thickened but mobile pulmonary valves seen at angiography and none had more than mild dilatation of the main pulmonary artery. One of the 2 children with Noonan's syndrome had a thickened, myxomatous valve at subsequent surgery, while the other had no angiographic evidence of this change. Angiography was also used to assess qualitatively the presence and degree of infundibular hypertrophy.

Results

The pertinent clinical and catheterization data are given in Table 1. Fig. 1 shows how the right ventricular systolic pressure changed at subsequent catheterizations and, since pulmonary arterial pressures in pulmonary stenosis do not vary much, also represents the changes in peak systolic pressure difference across the right ventricular outflow tract. There was a tendency for the right ventricular systolic pressure to rise, especially in younger children and those with higher initial pressures. Of 25 first catheterized under 5 years of age, pressure rose in 17 (over 20 mmHg (2.7 kPa) in 11), fell in 6, and rose and then fell in 2. The falls of pressure were under 20 mmHg (2.7 kPa) in all but 2 children, in 1 of whom a left-to-right atrial shunt disappeared spontaneously between the 2 studies. A systolic pressure rise over 20 mmHg (2.7 kPa) was noted in 2 out of 7 and in 7 out of 12 whose initial right ventricular systolic pressures were, respectively, under 50 and between 51 and 100 mmHg (6.7 and 13.3 kPa). The difference was not significant ($P=0.18$) by Fisher's exact test. Of 10 children first catheterized over 5 years of age, right ventricular systolic pressure rose in 7 (in 4 it rose less than 20 mmHg (2.7 kPa)) and fell less than 10 mmHg (1.2 kPa) in 3. The smaller rise of pressure in those first studied over 5 years is all the more striking because they usually had the greater time intervals between catheterizations.

A major cause of a change in right ventricular systolic pressure between studies is a change in stroke volume; this usually increased with age and growth and could have been increased or decreased by differences in sedation and anxiety. The two variables tended to rise together but could at times vary in opposite directions (Fig. 2).

We measured changes in right ventricular systolic ejection time in 23 patients; in 7 there was a slight decrease at the second study of 0.01 to 0.08 s, in 3 there was no change, and in 13 ejection time increased up to 0.19 s, with a mean increase of 0.066 s. Only 3 of the 23 measurements had ratios of ejection

TABLE I *Serial catheterization and electrocardiographic data*

Case No.	*Age*	*BSA (m^2)*	*Pressures (mmHg)*				*Sa O_2* (%)	*AV O_2 difference* (*ml/l*)	*Qv* (*l/min per m^2*)	*HR*	*SV* (*ml*)
			a	*RA mean*	*RV*	*MPA*					
1	1 d	0.18	10	8	72/6	58/44		28	4.7	180	5
	18 d	0.18			96/6	78/22				180	
	64 d	0.23	6	4	100/6	52/29		24	5.8	120	11
2	4 d	0.11	0	−2	72/–		89	61	2.6	160	1.8
	18 d	0.11	2	−2	102/–		86	48	3.2	140	2.5
	1 yr 1 m	0.40	14	7	200/6	16/8	89	58	2.4	108	9
3	5 d	0.16	1	0	32/0	26/7	97	22	3.9	150	4
	1 yr 2 m	0.44	6	3	75/6	37/8	99	30	5.0	120	18
4	10 d	0.19	6	1	95/6	32/10	94	33	4.0	160	4.8
	1 yr 4 m	0.42	8	4	45/6	24/12	97	41	3.2	120	11
5	3 w	0.23	2	1	38/–	22/–		20	7.5	120	14
	1 yr 1 m	0.46	8	5	50/7	24/16	95	17	5.4	120	21
6	6 w	0.27	11	6	190/10		98	22	5.9	150	11
	4 m	0.33	12	5	175/8		98	43	3.0	150	7
7	2½ m	0.30	4	1	70/–	9/5	95	44	3.2	150	6
	10 m	0.47			106/–	16/4	95	24	6.2	120	24
	2 yr 6 m	0.58	7	6	75/8	23/14	98	25	6.0	140	25
8	4 m	0.31	8	6	76/10	25/15		35	3.7	150	8
	1 yr ½ m	0.55	11	8	110/12	30/19		20	7.5	120	34
	3 yr	0.80			60/3	24/5				90	
9	5 m	0.40	3	1	38/1	25/9				150	
	3 yr	0.54	10	8	50/6	12/6	93	23	6.5	100	35
10	5 m	0.32	6	5	85/4	20/10	93	36	3.6	136	8.5
	1 yr 5 m	0.52	7	4	100/6	16/8	94	40	4.1	116	18
11	5 m	0.41	7	4	104/6	16/8	96	43	3.5	115	12
	1 yr 4 m	0.52	11	6	130/8	14/4	96	40	3.7	120	16
	1 yr 11 m	0.55	14	8	192/12	17/13	97	66	2.3	120	11
12	6 m	0.45	10	4	110/4		92	78.5	1.9	150	5
	10 m	0.40			140/8						
13	7 m	0.25		4	82/8	16/10	90	27	5.6	144	10
	2 yr 2 m	0.50	10	7	160/6	13/8	93	38	4.0	110	18
14	1 yr	0.56	8	6	59/8	22/12	96	21	7.1	140	28
	4 yr	0·70	8	6	80/10	18/10	93	44.5	3.4	100	24
15	1 yr 4 m	0.49	2	1	110/10	16/9	93	37	4.3	160	13
	2 yr 1 m	0.49	5	4	90/10	15/8	95	42	3.6	120	15
	4 yr	0.81			83/8	20/11				100	
16	1 yr 6 m	0.42			40/2	16/6		28			
	4 yr 6 m	0.68			55/8	14/10		28·5	5.3	110	33
17	2 yr 4 m	0.58	5	4	145/6		85	78	1.9	140	8
	3 yr	0.58	14	8	130/12	16/8	79	60	2.5	120	12
18	2 yr 6 m	0.58	10	3	102/6	14/9	97	32	4.7	125	22
	4 yr	0.67	10	5	120/6	17/10	96	32	4.7	135	23
19	3 yr	0.64	0	2	76/6	15/10	96	46.5	3.6	120	19
	5 yr	0.80	7	2	108/12	23/10	95	37.5	3.7	75	40
20	3 yr	0.62	5	3	48/6	18/8	98	32	5.0	96	32
	6 yr	0.83	8	4	100/12	22/10	92	32	4.8	96	42
21	3 yr	0.55	8	7	63/10	22/10		44	3.5	90	21
	8 yr 11 m	0.90	11	8	75/11	22/10	98	37	4.0	80	45
22	3 yr	0.70			32/6	21/8					
	10 yr	1.60	3		23/3	13/5	96	38	3.8	85	72
23	3 yr 6 m	0.65	7	5	80/7	27/9	99	44	3.4	94	24
	10 yr	1.12	8	7	105/14	28/10	98	50	2.7	86	35

SET (s)	*VA (cm^2)*		*Electrocardiogram*			*Other*
	Absolute	*per m^2 BSA*	*P*	*R*	*QRS axis*	
0.21	0.14	0.88		20	140	Rubella; peripheral pulmonary stenosis; PDA; L-R atrial shunt; Qp:Qs = 1.8
0.24				27	140	No PDA, L-R atrial shunt only on angiogram
0.24	0.14	0.65		13	140	No shunts
0.32	0.02	0.17				
0.30	0.02	0.21		8	180	
0.27	0.06	0.16				Infundibular hypertrophy; R-L atrial shunt
0.22	0.20	1.4		24	60	Rubella
0.26	0.30	0.7		14	85	
0.19	0.10	0.50	n	6	105	
0.30	0.21	0.50	+	17	135	No shunt
0.20	0.44	1.93		13	130	Small PDA; Qp:Qs 1.3
0.24	0.45	0.97		22	30	No shunt
	0.08+	0.28+	+	19	110	Infundibular hypertrophy
	0.06+	0.18+	±	26	140	Infundibular hypertrophy
0.26	0.12	0.35				
0.26	0.18	0.40		20	200	
0.28	0.40	0.65		13	170	
0.20	0.15	0.46		12	60	
0.20	0.50	0.91		6	80	
0.30				11	75	
0.20						
	0.58+	1.07+				
0.26	0.10	0.32				L-R atrial shunt; Qp:Qs = 1.2
0.26	0.21	0.41				L-R atrial shunt; Qp:Qs = 1.2
0.23	0.11	0.28				
0.29	0.13	0.25	+	20	120	
0.36	0.06	0.11				Infundibular hypertrophy
0.30	0.04	0.10	+	22	180	R-L atrial shunt
			+ +	24	200	
0.26	0.13	0.52				Noonan's syndrome; R-L atrial shunt
0.31	0.11	0.22				Severe infundibular hypertrophy
	0.57+	1.01	n	4	90	
0.30	0.23	0.33	±	6	110	Infundibular hypertrophy
0.20	0.19	0.36				
0.25	0.18	0.36				
0.32			n	8	n	
				9	110	Hypothyroid
0.30	0.34	0.50	±	3	100	
0.21	0.09	0.15	n			R-L atrial shunt; infundibular hypertrophy
0.22	0.09	0.15	n	19	I	R-L atrial shunt; infundibular hypertrophy
0.27	0.24	0.42				
0.26	0.30	0.44				
0.21	0.32	0.50	n	19	110	
0.40	0.30	0.37	+	23	110	
0.20	0.71	1.15	n	6	100	Slight infundibular hypertrophy
0.30	0.41	0.49	+	12	150	Severe infundibular hypertrophy
0.36	0.24	0.45	n	12	75	
0.28	0.59	0.66	n	8	95	
0.20	1.92	1.20				
0.30	0.28	0.44	n	12	120	
0.28	0.44	0.39			140	

TABLE I (Cont'd)

Case No.	*Age*	*BSA (m^2)*	*Pressures (mmHg)*				*SaO_2%*	*AV O_2 difference (ml/l)*	*Qv (l/min per m^2)*	*HR*	*SV (ml)*
			a	*RA mean*	*RV*	*MPA*					
24	4 yr	0.68			54/3	13/6	98	29	5.5	100	37
	14 yr 6 m	1.70	12	5	90/10	20/10	95	44	3.6	72	85
25	4 yr 9 m	0.76	7	3	35/8	20/7	95	41	3.8	82	35
	13 yr 9 m	1.42	8	4	32/8	22/8	95	50	3.4	85	57
26	5 yr	0.75	10	2	80/6	25/6	97	39	4.1	100	30
	10 yr	1.18	7	3	95/8	18/6	95	29	5.2	80	76
27	5 yr 7 m	0.79		5	60/5	15/10	98	39	4.1	120	27
	13 yr	1.43	7	5	55/9	18/8	94	41	5.1	70	105
28	6 yr	0.80	6	3	60/6	26/8	95	24	6.9	120	46
	8 yr	0.95	11	6	100/8	19/7	94	37	4.1	100	39
29	6 yr	0.78			66/9	20/9	96	44	3.6	100	28
	14 yr	1.29	7	3	80/9	20/10	99	63	2.3	70	42
30	6 yr	0.90			19/0	11/3					
	17 yr	1.75	4	3	25/4	15/5	95	40	3.4	80	74
31	6 yr 3 m	0.86			48/2	12/5					
	13 yr	1.40	7	3	75/7	15/5	98	46	2.6	60	60
32	7 yr	0.80	9	5	60/10	31/18	94	35	4.5	110	33
	12 yr	1.40	3	1	80/4	18/12	94		4.6	90	72
33	7 yr	0.96			29/1	11/6			3.5	114	23
	17 yr	1.82	11	1	21/4	12/5	96	46	2.9	75	70
34	7 yr	0.74	6	3	46/6	15/4	98	34	4.4	100	44
	18 yr	1.42	11	5	60/12	30/12	96	23	6.2	100	88
35	9 yr	0.94	5	3	65/7	15/10	96	27	5.2	107	48
	15 yr	1.53	12	5	60/8	22/10	93	40	3.8	94	62

Pressures: RA = right atrium; RV = right ventricle; MPA = main pulmonary artery; SaO_2 = arterial oxygen saturation; AV O_2 difference = arteriovenous oxygen difference; Qv = pulmonary valve flow; HR = hear rate; SV = stroke volume; SET = right ventricular ejection time; VA = pulmonary valve area (+ indicates area calculated from resistance).
Electrocardiogram: (P wave) n = normal; + = increased; ± = borderline; (mean frontal axis) RAD = right axis deviation; I = indeterminate axis, n = normal; (R wave) R = height of R wave in mm in V1 or V4R.
PDA = persistent ductus arteriosus.
Conversion factor from Traditional to SI units: 1 mmHg ≈ 0.133 kPa.

times (second study divided by first study) between 1.5 and 2.0, 10 had ratios from 1.05 to 1.26, and in 10 the ratio ranged from 0.74 to 1.0. The increases in ejection time were caused mainly by slower heart rates and older ages at the second study (Golde and Burstin, 1970).

Fig. 3A shows that calculated absolute valve orifice area rose in 20 (over 100% increase in area in 10, from 50 to 99% increase in 5, and under 50% increase in 5); the area was unchanged in 4 and it fell in 8 (by less than 25% in 4 and by 26 to 50% in 4). The increases in orifice area often did not keep pace with the increase in body surface area. Valve orifice area per square metre of body surface area (Fig. 3B) rose in 12 (over 100% increase in 1 only, 50 to 99% in 2, and less than 50% in 9), was unchanged in 3, and fell in 17 (by less than 25% in 9, and more than 50% in 4).

Most of the striking decreases in the calculated orifice area were associated with infundibular hypertrophy.

The body surface areas of almost all the children were within normal limits and the 4 who were below the 3rd percentile at the first study were close to the 50th percentile at the second study. Most children grew at a normal rate, unrelated to the severity of the pulmonary stenosis, except for 2 with very severe stenosis and congestive heart failure.

The *x*-rays of the heart and chest were not helpful. None with mild or moderate stenosis had increased cardiothoracic ratios, though most had

SET (s)	*VA (cm^2)*		*Electrocardiogram*			*Other*
	Absolute	*per m^2 BSA*	*P*	*R*	*QRS axis*	
	0.50+	0.74+	n	7	75	
0.30	0.73	0.43	+	14	120	
0.35	0.60	0.79				
0.30	1.25	0.88	n	17	I	
	0.34+	0.45+			RAD	
0.30	0.72	0.61	+	12	130	Infundibular hypertrophy
0.26	0.41	0.51	n	18	135	
0.26	1.80	1.30	n	10	135	
	0.74+	0.93+		12		
0.22	0.50	0.53	n		110	Infundibular hypertrophy
0.32	0.34	0.44	n	15	120	
0.40	0.40	0.31	+	18	180	
			n	2	n	
0.25	2.63	1.5	n	6	n	
			n	4	80	
0.42	0.56	0.40	+	11	120	
	0.70+	0.88+				
0.30	0.70	0.50	n	12	50	Infundibular hypertrophy
	0.74+	0.97+	n	3		
0.30	2.36	1.30	n	3	105	
	0.65+	0.88+				Noonan's syndrome
0.37	1.09	0.77				
0.35	0.56	0.60				
0.26	0.99	0.65	n	6	115	

a cardiac contour that suggested right ventricular hypertrophy. Most had post-stenotic dilatation of the main pulmonary artery. No significant changes took place with time, even in the patients with increasing right ventricular systolic pressure. The 3 children with the severest stenosis and symptoms had right atrial and ventricular enlargement as well as an increased cardiothoracic ratio.

In the electrocardiogram, normal P waves became peaked and tall in 8 patients whose right ventricular systolic pressures rose by 14 to 50 mmHg (1.9 to 6.7 kPa) to reach pressures of 55 to 140 mmHg (7.3 to 18.6 kPa). However, in another 6 children the P waves remained normal despite 9 to 40 mmHg (1.2 to 5.3 kPa) rises of right ventricular systolic pressure to levels of 65 to 105 mmHg (8.6 to 14.0 kPa).

In 19 children the frontal plane QRS axis was recorded at each cardiac catheterization and in another 10 it was recorded once. Most of the QRS axes were over 90°. In general the QRS axis and the right ventricular systolic pressure rose or fell together, but on 5 occasions one variable rose while the other fell (Fig. 4A). The height of the R or R′ wave in the right praecordial leads usually changed in the same direction as the change in right ventricular systolic pressure (Fig. 4B) but 6 cases were exceptions. These were not related to right ventricular conduction disturbances nor to age; the children with Noonan's syndrome are not included in these figures.

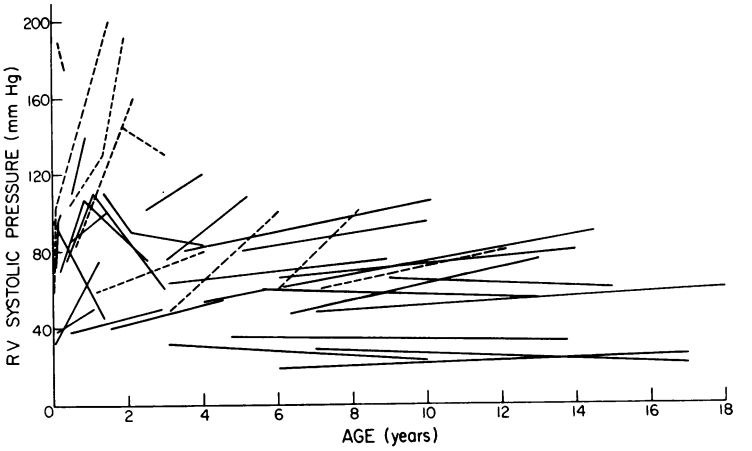

FIG. 1 *Changes in right ventricular systolic pressure with age. The straight lines here and in subsequent figures join points in the same patient and do not indicate a linear change. Dashed lines show those with infundibular hypertrophy.*

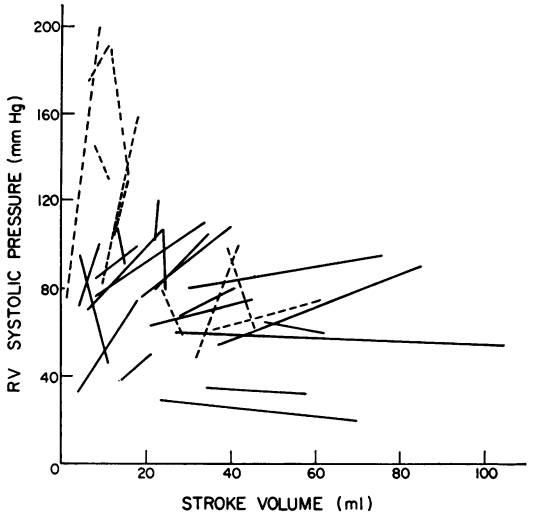

FIG. 2 *Relation of stroke volume and right ventricular systolic pressure in repeat catheterizations. Dashed lines show those with infundibular hypertrophy.*

Discussion

Calculations

Estimating pulmonary valve orifice area from the Gorlin formula is subject to errors in the measurement of each component of the formula, but the contribution to the total error varies for each component. The mean systolic pressure drop from right ventricle to pulmonary artery is usually measured with reasonable accuracy and, since the square root of this difference is taken, errors in the measurement have little effect on the calculated valve area. Furthermore, a high correlation between mean and peak systolic pressure difference across the pulmonary valve has been shown by Bassingthwaighte *et al.* (1963) and by Campbell (1960). Therefore, we believe that there was negligible error in deriving mean from peak pressure differences on the few occasions when the original tracings were not available.

Systolic ejection times are more difficult to measure at cardiac catheterization when pressures are not recorded with high fidelity. However, our repeated measurements of pressure tracings by different observers and comparisons of these measurements with phonocardiograms in 2 patients suggested that the error of measuring right ventricular systolic ejection time was no more than 20 per cent.

The major source of error lies in calculating stroke volume when oxygen uptake is not measured. Almost all the calculated high cardiac outputs were associated with low arteriovenous differences of oxygen content, however, suggesting that indeed the flows were higher than normal. Finally, increases in right ventricular pressure and right-sided forces were well correlated, so that the pressure increases were in general not caused by transiently raised stroke volumes. It is notable that many other published studies also relied on assumed oxygen consumption.

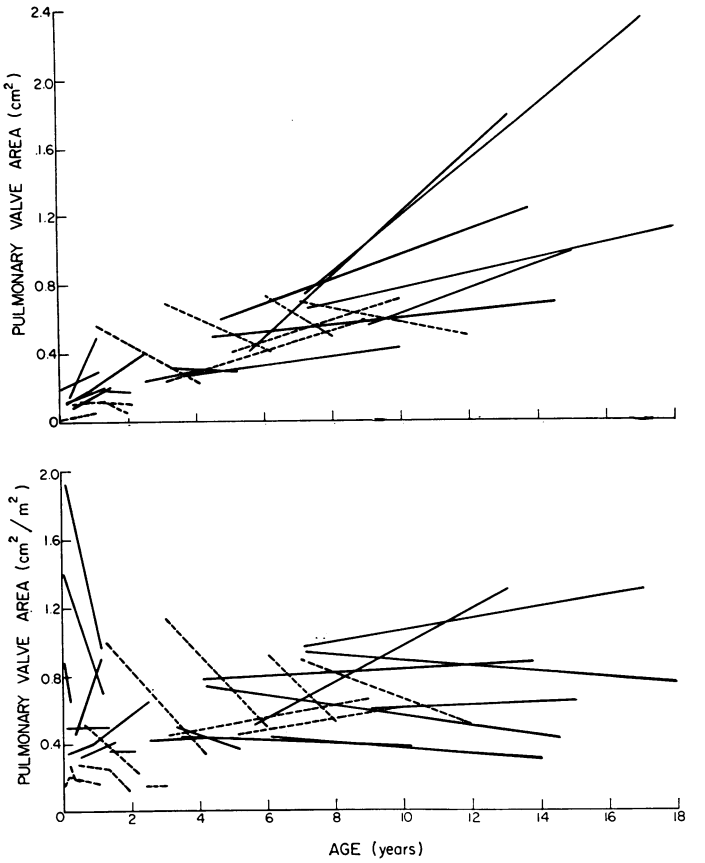

FIG. 3 *A) Upper panel: change in absolute pulmonary valve area (or equivalent area) with age. B) Lower panel: change in pulmonary valve area (or equivalent area) per square metre of body surface area with age. Dashed lines show those with infundibular hypertrophy.*

Pressure changes

As described by Gorlin and Gorlin (1951), A = flow per systolic second/44.5 $\sqrt{\Delta P}$, where A is the valve orifice area and ΔP is the mean systolic pressure drop from right ventricle to main pulmonary artery. Since flow per systolic second is stroke volume (SV) divided by right ventricular systolic ejection time (SET), the formula can be rearranged to give $\Delta P = [(SV/SET)/44.5A]^2$. Increases in right ventricular systolic pressure are thus caused by an increase in the ratio $[(SV/SET)/A]^2$. With normal growth, cardiac output increases approximately in proportion to body surface area (Cayler, Rudolph, and Nadas, 1963; Jegier *et al.*, 1963), though recent studies suggest a slightly better correlation with height alone (Krovetz and Goldbloom, 1972). Because of the normal slowing of heart rate from infancy to adulthood (Liebman, 1968; Walsh, 1968) stroke volume increases more rapidly than does cardiac output so that there is about a twelve- to fifteenfold increase of stroke volume from birth to adult life. At the same time, the increase in age and decrease of heart rate would be expected to increase systolic ejection time between two- and threefold (Golde and Burstin, 1970). Thus, for a fixed valve orifice area, the ratio of SV/SET would normally rise four- to sevenfold from birth to adult life, and in theory, cause sixteen- to forty-ninefold rise in mean systolic pressure difference from right ventricle to pulmonary artery. That this does not occur is because of the additional prolongation of right ventricular ejection time from the pulmonary stenosis (Vogelpoel and Schrire, 1960; Gamboa, Hugenholtz, and Nadas, 1964), to increase in size of the valve orifice, or to congestive failure. In some patients with severe pulmonary stenosis right

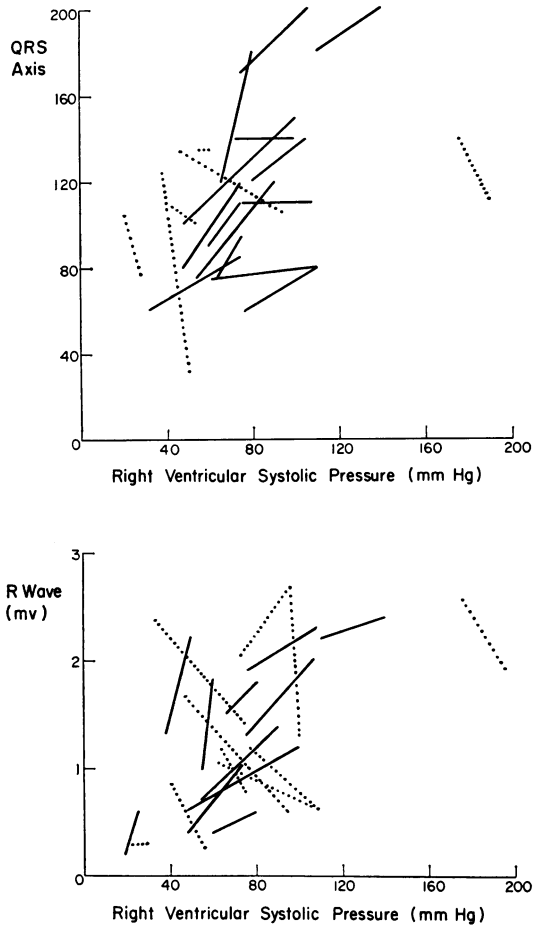

FIG. 4 *Change in right ventricular systolic pressure and A) change in frontal plane QRS axis or B) change in height of R or R' wave in V1 or V4R, whichever is largest. Dotted lines show grossly inappropriate changes.*

ventricular systolic pressure does not increase much because a right-to-left atrial shunt decreases right ventricular stroke volume.

Although absolute valve orifice area usually increased with age, it seldom increased more than and often grew much less than body surface area. This suggests restricted growth of the stenotic valve, and confirms the hypothesis of Engle and Taussig (1950). Moller and Adams (1965) and Lueker *et al.* (1970) found valve area to increase in proportion to body surface area; however, their patients were older and did not show increases in right ventricular systolic pressure. Absolute decreases of calculated orifice area seemed to be caused usually by infundibular hypertrophy rather than by narrowing of the valve orifice. In our small series, severe infundibular hypertrophy occurred in patients before 2 years of age; in these children right ventricular systolic pressures were initially over 70 mmHg (9.3 kPa). However, one boy at 3 years of age had mild infundibular hypertrophy with a right ventricular systolic pressure of 48 mmHg (6.4 kPa); by 6 years of age the pressure had risen to 100 mmHg (13.3 kPa) and there was severe infundibular hypertrophy.

The results of our study show that right ventricular pressures often increased, particularly in young children, and that in young children the chance of increase was independent of initial pressure levels (Table 2A). By contrast, analysis of published cases suggests that increases in pressure are uncommon and occur predominantly in those over 5 years old when first catheterized (Table 2B). Consequently, either the existing reports give too optimistic a prognosis or our data err in being too pessimistic. One of the difficulties in deciding between these alternatives is that there is considerable selection involved. It is likely that many children of all ages with clinically mild and stable pulmonary stenosis are not catheterized or recatheterized. On

TABLE 2 *Numbers of children arranged by age and right ventricular systolic pressure at first cardiac catheterization*

Initial right ventricular systolic pressure (mmHg)		*Age at first study (yr)* <5	5 to 15	>15
A				
50 or less	*6.7* or less	7 (2)	4 (1)	
51 to 75	*6.8–10.0*	6 (4)	5 (2)	
76 to 100	*10.1–13.3*	6 (3)	1 (0)	
101 or more	*13.4* or more	6 (2)	0 (0)	
		25 (11)	10 (3)	
B				
50 or less	*6.7* or less	2 (0)	19 (1)	8 (0)
51 to 75	*6.8–10.0*	9 (0)	29 (2)	5 (0)
76 to 100	*10.1–13.3*	2 (0)	12 (5)	3 (2)
101 or more	*13.4* or more	2 (1)	9 (3)	5 (1)
		15 (1)	69 (11)	21 (3)

Numbers in parentheses indicate those whose pressures had risen 20 mmHg (2.7 kPa) or more at the second study. *A)* Data from present study. *B)* Data from reported studies (Fabricius, 1959; Engle *et al.*, 1964; Tinker *et al.*, 1965; Levine and Blumenthal, 1965; Moller and Adams, 1965; Loogen *et al.*, 1966; Lueker *et al.*, 1970; Møller *et al.*, 1973). Figures in italics are pressures in kPa.

the other hand, children who have high right ventricular systolic pressures when young either die or are operated on, and so would not appear in the later phases of any natural history study. Furthermore, it is only relatively recently that serial catheterizations in infants with pulmonary stenosis have been reported; there are 13 first studied under 1 year of age in our series, and none in the series collected from the published reports. While a randomized, prospective study will be necessary to define the risk of increasing severity of pulmonary stenosis at each stage and initial pressure, it is clear from our data that significant increases may be commoner in very young children than is presently reported.

While our series does not give accurate estimates of the risk of increases in severity of pulmonary stenosis, it does allow some prognostication. An infant with a moderately high or high right ventricular systolic pressure caused by pulmonary stenosis has a small absolute valve orifice area, with a valve that is probably thick and, therefore, not likely to grow adequately; with growth and increase of stroke volume the pressure is likely to rise considerably, and the rise will be accentuated if infundibular stenosis develops. The older child with only slightly raised right ventricular systolic pressure has at that time a reasonably large valve orifice, the valve is probably only slightly thickened and thus perhaps capable of growing well, and there will be relatively little further increase of stroke volume.

The factors that cause the right ventricular pressure to rise or remain constant appear to be similar in those with typical valvar pulmonary stenosis and in those with added mild peripheral pulmonary arterial stenosis or even those with Noonan's syndrome. One child with Noonan's syndrome had an orifice area that kept pace with body growth, so that right ventricular pressure rose only slightly from 7 to 18 years, while the other, who had a myxomatous valve, developed a rapid and striking rise of right ventricular systolic pressure related mainly to the development of conspicuous infundibular hypertrophy at an early age.

Since it is not yet possible to predict the course of this lesion in young children, they should be followed carefully to determine whether cardiac catheterization is needed or should be repeated. Body growth is normal (Fabricius, 1959) and the children are usually asymptomatic unless the stenosis is extremely severe. Radiological changes are not sensitive indicators of early increases of severity. The phonocardiogram is likely to be a better method of following the severity of pulmonary stenosis (Vogelpoel and Schrire, 1960; Gamboa *et al.*, 1964), though no one has confirmed this, especially in very young children. It is also possible that the echocardiogram may eventually prove a useful tool. At present, however, the most commonly used indirect method of assessing the severity of pulmonary stenosis is the electrocardiogram (Cayler, Ongley, and Nadas, 1958; Fabricius, 1959; DePasquale and Burch, 1960; Bassingthwaighte *et al.*, 1963; Engle and Goldberg, 1964; Hugenholtz and Gamboa, 1964), since in pulmonary stenosis there is a good correlation between the height of the R wave in the right chest leads (V1 or V4R) and the right ventricular systolic pressure. Usually, however, these results have not been obtained by serial studies. Furthermore, despite the good correlation coefficients, the variability about the regression line is considerable and usually not commented on. As a result of this variability, the prediction of right ventricular systolic pressure from the height of the R wave in V1 or V4R is subject at times to large errors; the important error of missing severe or increasing stenosis because it is not reflected in the electrocardiogram has been stressed by Boyle, Morton, and Pantridge (1964). Our results of serial studies in the same patient confirm not only the tendency for the height of the R wave to reflect the right ventricular systolic pressure but also the variability of this relation and the possibility of missing an increase in severity by relying only on the electrocardiogram.

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